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| 10/588,186 | 08/02/2006 | Laurence Hermitte | 0528-1187 | 6791 |

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| EXAMINER | |
|---|---|
| BROWE, DAVID | |
| ART UNIT | PAPER NUMBER |
| 1617 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DocketingDept@young-thompson.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/588,186 | HERMITTE ET AL. | |
| | Examiner | Art Unit | |
| | DAVID M. BROWE | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *21 and 25* is/are allowed.

6)☒ Claim(s) *1-20,22 and 23* is/are rejected.

7)☒ Claim(s) *24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Request for Continued Examination*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and submission filed on December 3, 2010, that includes a response to the Final Office Action mailed on June 3, 2010, have been entered. Claims 1-4 and 10-11 have been amended; claims 21-25 have been newly added; and no claims have been cancelled. Claims 1-25 are pending in the application and are currently under examination.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 1-20 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ågerup (U.S. Patent No. 5,827,937), in view of Miller *et al.* (U.S. Patent No. 6,174,999).**

***Applicant Claims***

Applicants claim a process for the production of a biocompatible crosslinked polydensified monophasic gel comprising: *a)* starting a crosslinking reaction of a predetermined quantity of at least one biocompatible polymer in solution by the addition of a quantity of crosslinking agent in a first volume of a reaction mixture; *b)* crosslinking said quantity of polymer; *c)* diluting the reaction mixture to decrease the overall concentration of polymer in a second volume of the reaction mixture, and adding a supplemental quantity of polymer of a molecular weight higher than 500,000 Da in an amount of 10% in solution; *d)* continuing crosslinking in the second volume of the

reaction mixture; and *e)* stopping the crosslinking reaction by eliminating the crosslinking agent. The crosslinking reaction can be initiated in a basic or acidic medium; a supplemental quantity of crosslinking agent is added prior to step *c)*; and the step of stopping the crosslinking reaction is carried out by dialysis. The polymers are of natural origin and selected from the group consisting of hyaluronic acid, chondroitin sulfate, keratin, keratin sulfate, heparin, heparin sulfate, cellulose and its derivatives, alginates, xanthane, carrageenan, proteins, and nucleic acids, wherein at least one polymer not naturally present in the human body is crosslinked with at least one polymer naturally present in the human body. The crosslinking agent is a bifunctional or polyfunctional molecule comprising components selected from the group consisting of epoxys, epihalohydrins, and divinylsulfone.

Applicants also claim a biocompatible crosslinked polydensified monophasic gel prepared by the said process that comprises at least one dispersed active agent therein. The degree of crosslinkage varies, and comprises crosslinked hubs interconnected by gel having a quantity of crosslinkage that progressively decreases from that of the hubs.

Applicants further claim a method to separate, replace, or fill a biological tissue or increase the volume of said tissue or to supplement or replace a biological fluid, comprising injecting the gel into said tissue.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

Ågerup discloses a process for the production of a biocompatible crosslinked gel comprising: *a)* starting a crosslinking reaction of a predetermined quantity of at least

one biocompatible polymer in solution by the addition of a quantity of crosslinking agent; *b)* crosslinking said quantity of polymer; and *c)* diluting the reaction mixture to decrease the concentration of polymer in solution, and supplementing the polymer concentration in solution, thereby accelerating the rate of the crosslinking reaction; and *d)* crosslinking to a viscoelastic gel (Col. 1, lns. 4-12; Col. 2, lns. 11-15, 48-67; Col. 3, lns. 1-2, 25-60; Col. 4, lns. 1-3, 6-30). The crosslinking reaction can be initiated in a basic or acidic medium, and the step of increasing the polymer concentration and crosslinking reaction rate need not necessarily proceed under the exact same conditions as when initiating the crosslinking (Col. 3, lns. 32-40; Col. 4, lns. 22-30), implying that a polydensified gel is being produced. The polymers can be of natural origin and selected from the group consisting of hyaluronic acid, chondroitin sulfate, keratin, keratin sulfate, heparin, heparin sulfate, cellulose and its derivatives, alginates, xanthane, carrageenan, proteins, and nucleic acids, wherein at least one polymer not naturally present in the human body is crosslinked with at least one polymer naturally present in the human body (Col. 4, lns. 1-3, 6-9; Col. 7, lns. 21, 35, 48-49, 58-59). The crosslinking agent is a bifunctional or polyfunctional molecule comprising components selected from the group consisting of epoxides, such as epihalohydrins; and divinylsulfone (Col. 4, lns. 10-21).

Ågerup also discloses a biocompatible polydensified gel prepared by the process that *i)* comprises at least one dispersed active agent, *ii)* can exhibit a variable degree of cross-linkage, and *iii)* is used to separate, replace, or fill a biological tissue or increase the volume of said tissue or else to supplement or replace a biological fluid (Col. 2, lns. 17-19, 24-38; Col. 4, lns. 49-55; Col. 5, lns. 49-60; Col. 6, lns. 12-24).

Ågerup further discloses a method to separate, replace, or fill a biological tissue or increase the volume of said tissue or to supplement or replace a biological fluid, comprising administering the gel into said tissue (Col. 4, lns. 34-36; Col. 6, lns. 12-24).

Miller *et al.* disclose a process of preparing a biocompatible crosslinked polysaccharide gel that includes stopping a reaction by eliminating a non-polymeric reactant from the reaction medium by dialysis, according to standard practice, prior to use (Col. 1, lns. 13-15; Col. 2, lns. 32-36; Col. 6, lns. 39-42).

***Ascertainment of the Difference Between the Scope of the Prior Art and the Claims (MPEP §2141.012)***

Ågerup does not explicitly disclose a crosslinking process that specifically includes *i)* adding supplemental quantities of polymer and crosslinking agent to the diluted reaction medium and *ii)* stopping the reaction specifically by dialysis. These deficiencies is cured by the teaching of Ågerup and Miller *et al.*

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to combine the respective teachings of Ågerup and Miller *et al.* outlined *supra* to devise applicants claimed invention. Ågerup discloses a process for preparing a biocompatible cross-linked gel utilizing a dilution-concentration cross-linking technique that enables more optimal control of cross-link coupling site architecture; the gel products thus produced do not cause interfering or negative volume effects when administered in vivo, and better retain and provide sustained-release

delivery of active substances. Since Ågerup specifies that diluting the reaction mixture to decrease the concentration of polymer in solution is accompanied by supplementing the polymer concentration in solution and accelerating the rate of the cross-linking reaction; and since Miller *et al.* disclose the step of preparing purified polymer mixtures, for direct use in drug delivery, by eliminating unreacted "activating agent" by dialysis, one of ordinary skill in the art would be motivated to devise a cross-linking reaction that specifically included *i)* adding supplemental quantities of polymer and cross-linking agent to the diluted reaction medium (thus, achieving increased polymer concentration and accelerated rate of cross-linking) and *ii)* stopping the reaction specifically by dialysis, with the reasonable expectation that such a technique would successfully produce a cross-linked biocompatible gel in optimal purified condition for direct *in vivo* use in providing a better sustained-release drug delivery profile without causing any interfering or negative volume effects.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Response to Arguments***

Applicant's arguments filed April 20, 2010 have been fully considered but they are not persuasive.

*i)* Applicant asserts that "the presently claimed process is distinct from the AGERUP process".

Respectfully, though, the Examiner, from the disclosure of Ågerup alone, cannot agree with the assertion that Ågerup fails to teach or suggest applicant's claimed process. Ågerup teaches a process that includes combining biocompatible polymer and crosslinking agent, cross-linking the polymer, overall dilution, and continuing the cross-linking reaction. Ågerup explains that "stearically hindering" means diluting the reaction mixture; this need not stop the reaction, only lower the concentration of polymer (Col. 3, lns. 25-30, 43-47). Re-introducing "stearically unhindered" conditions, according to Ågerup, should be "interpreted broadly" to mean anything that accomplishes a higher concentration of the polymer in said medium and enables a more rapid reaction to take place relative to the stearically hindered condition (Col. 3, lns. 32-33, 37-39, 52-53). Although Ågerup suggests, as particular examples, increasing polymer concentration by evaporating or dialyzing the aqueous medium, one of ordinary skill in the art would recognize that accomplishing a higher concentration of the polymer (relative to the "sterically hindered" condition) can also be done simply by adding more polymer (i.e. adding a supplemental quantity of polymer), and that enabling a more rapid reaction can be done by adding more polymer and more cross-linking agent. Agerup further provides that even after introducing "stearically unhindered" conditions, the net effect relative to

the original conditions could be a dilution of the reaction so as to decrease the overall concentration of polymer in a second volume of reaction mixture.

*ii)* Applicant asserts that "*AGERUP creates sterically hindered conditions to essentially stop the first cross-linking reaction*".

Respectfully, however, the Examiner cannot agree. According to Agerup, "sterically hindering the cross-linking reaction should be interpreted in a broad sense"; that "what is important is that the rate of cross-linking is substantially reduced", and that "sterical hindrance comprises diluting the aqueous medium". Thus, Agerup is diluting the reaction medium, and this should slow, but does not necessarily completely stop, the cross-linking process.

*iii)* Applicant asserts that "*While the AGERUP method produces what is described as a 'biphasic' gel having hyaluronic acid 'chunks', the presently claimed method produces a 'monophasic' gel having a 'spider web' network*".

The Examiner, however, cannot agree that the Agerup method cannot be used to produce a monophasic gel. As stated in part *ii)* above, the dilution step serves to slow the cross-linking process, but does not necessarily stop it. Cross-linking is thus continued. Agerup does not appear to use the term "biphasic" to describe their gel.

For the foregoing reasons, the 35 USC rejection of claims 1-20 and 22-23 is hereby maintained.

***Allowable Subject Matter***

Claims 21 and 25 are allowed.

Claim 24 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Inquiries***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID M. BROWE whose telephone number is 571-270-1320. The examiner can normally be reached on Monday-Friday 7:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carlos A. Azpuru/
Primary Examiner, Art Unit 1617

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